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(54) Method for preparation of taxol using an oxazinone

Methode zur Herstellung von Taxol unter Verwendung von Oxazinon

Procédé pour la préparation du taxol utilisant une oxazinone

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(56) References cited:
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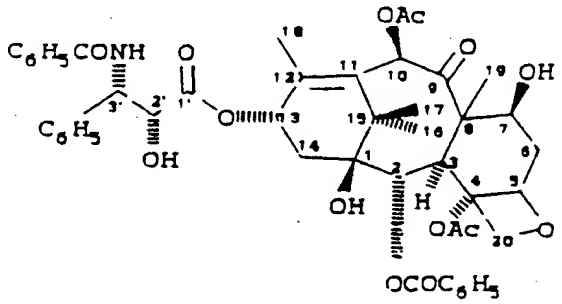
Description

BACKGROUND OF THE INVENTION

The present invention is directed to a novel oxazinone, a process for its preparation, and a process for the preparation of taxol involving the use of such oxazinone.

The taxane family of terpenes, of which taxol is a member, has attracted considerable interest in both the biological and chemical arts. Taxol is a promising cancer chemotherapeutic agent with a broad spectrum of antileukemic and tumor-inhibiting activity, having the following structure:

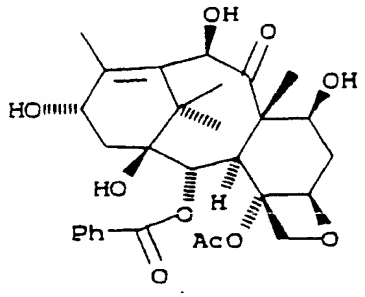


Because of this promising activity, taxol is currently undergoing clinical trials in both France and the United States.

The supply of taxol for these clinical trials is presently being provided by the bark from several species of yew. However, taxol is found only in minute quantities in the bark of these slow growing evergreens, causing considerable concern that the limited supply of taxol will not meet the demand. Consequently, chemists in recent years have expended their energies in trying to find a viable synthetic route for the preparation of taxols. So far, the results have not been entirely satisfactory.

One synthetic route that has been proposed is directed to the synthesis of the tetracyclic taxane nucleus from commodity chemicals. A synthesis of the taxol congener taxusin has been reported by Holton, et al. in JACS 110, 6558 (1988). Despite the progress made in this approach, the final total synthesis of taxol is, nevertheless, likely to be a multi-step, tedious, and costly process.

An alternate approach to the preparation of taxol has been described by Greene, et al. in JACS 110, 5917 (1988), and involves the use of a congener of taxol, 10-deacetyl baccatin III which has the structure shown below:



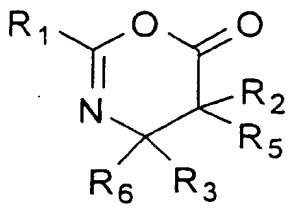
10-deacetyl baccatin III is more readily available than taxol since it can be obtained from the leaves of Taxus baccata. According to the method of Greene et al., 10-deacetyl baccatin III is converted to taxol by attachment of the C10 acetyl group and by attachment of the C13 β-amido ester side chain through the esterification of the C-13 alcohol with a β-amido carboxylic acid unit. Although this approach requires relatively few steps, the synthesis of the β-amido carboxylic acid unit is a multi-step process which proceeds in low yield, and the coupling reaction is tedious and also proceeds in low yield. However, this coupling reaction is a key step which is required in every contemplated synthesis of taxol or biologically active derivative of taxol, since it has been shown by Wani, et al. in JACS 93, 2325 (1971) that the presence of the β-amido ester side chain at C13 is required for anti-tumor activity.

A major difficulty remaining in the synthesis of taxol and other potential anti-tumor agents is the lack of a readily available unit which could be easily attached to the C13 oxygen to provide the β-amido ester side chain. Development of such a unit and a process for its attachment in high yield would facilitate the synthesis of taxol as well as related anti-tumor agents having a modified set of nuclear substituents or a modified C13 side chain. This need has been fulfilled by the discovery of a new, readily available, side chain precursor chemical unit and an efficient process for its attachment at the C13 oxygen.

SUMMARY OF THE INVENTION

Among the objects of the present invention, therefore, is the provision of a side chain precursor for the synthesis of taxols, and the provision of a process for the attachment of the side chain precursor in relatively high yield to provide a taxol intermediate.

Briefly, therefore, the present invention is directed to the use of a side chain precursor, an oxazinone 1 of the formula:



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wherein R_1 is C_{6-15} aryl, substituted C_{6-15} aryl, heteroaryl, C_{1-15} alkyl, C_{2-15} alkenyl, C_{2-15} alkynyl or OR_7 wherein R_7 is C_{1-15} alkyl, C_{2-15} alkenyl, C_{2-15} alkynyl, C_{6-15} aryl or heteroaryl; R_2 and R_5 are independently selected from hydrogen, C_{1-15} alkyl, C_{2-15} alkenyl, C_{2-15} alkynyl, C_{6-15} aryl, substituted C_{6-15} aryl, heteroaryl, and OR_8 wherein R_8 is C_{1-15} alkyl, C_{2-15} alkenyl, C_{2-15} alkynyl, C_{6-15} aryl, heteroaryl, or hydroxyl protecting group; and R_3 and R_6 are independently selected from hydrogen, C_{1-15} alkyl, C_{2-15} alkenyl, C_{2-15} alkynyl, C_{6-15} aryl, substituted C_{6-15} aryl, and heteroaryl.

In this specification the term "substituted C_{6-15} aryl" means C_{6-15} aryl substituted by at least one substituent selected from alkanoxy, hydroxy, halogen, alkyl, aryl, alkenyl, acyl, acyloxy, nitro and amido.

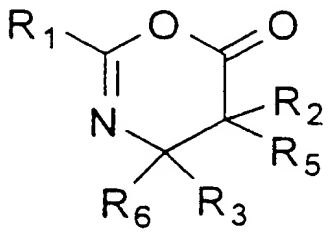
Specifically, the present invention is directed to a process for the preparation of a taxol intermediate comprising contacting an alcohol having the taxane tetracyclic nucleus and a C-13 hydroxyl group with an oxazinone of formula 1 in the presence of a sufficient amount of an activating agent to cause the oxazinone to react with the alcohol to form a β-amido ester which may be used as an intermediate in the synthesis of taxol.

The present invention is also directed to a process for the preparation of taxol which comprises contacting an alcohol having the taxane tetracyclic nucleus and a C-13 hydroxyl group with an oxazinone of formula 1 in the presence of a sufficient amount of an activating agent to cause the oxazinone to react with the alcohol to form a β-amido ester taxol intermediate. The intermediate is then used in the synthesis of taxol.

Other objects and features of this invention will be in part apparent and in part pointed out hereinafter.

DETAILED DESCRIPTION

The present invention is directed to the use of an oxazinone 1 and its derivatives, the structure of which is depicted hereinbelow.



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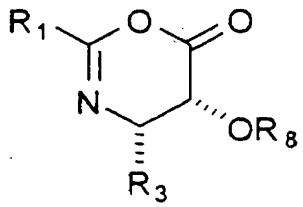
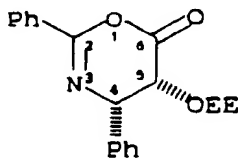
As noted above, R_1 is C_{6-15} aryl, substituted C_{6-15} aryl, heteroaryl, C_{1-15} alkyl, C_{2-15} alkenyl, C_{2-15} alkynyl or OR_7 wherein R_7 is C_{1-15} alkyl, C_{2-15} alkenyl, C_{2-15} alkynyl, C_{6-15} aryl or heteroaryl; R_2 and R_5 are independently selected from hydrogen, C_{1-15} alkyl, C_{2-15} alkenyl, C_{2-15} alkynyl, C_{6-15} aryl, heteroaryl, and OR_8 wherein R_8 is C_{1-15} alkyl, C_{2-15} alkenyl, C_{2-15} alkynyl, C_{6-15} aryl, heteroaryl, or hydroxyl protecting group; and R_3 and R_6 are independently selected from hydrogen, C_{1-15} alkyl, C_{2-15} alkenyl, C_{2-15} alkynyl, C_{6-15} aryl, substituted C_{6-15} aryl and heteroaryl.

The invention also relates to an oxazinone **1A** which has the structure



1A

wherein R_1, R_3 and R_8 are as previously defined. Most preferably R_8 is ethoxyethyl or 2,2,2-trichloroethoxymethyl. Thus, the structure of the most preferred oxazinone in which R_1 and R_3 are phenyl, R_5 is hydrogen and R_2 is R_8 with R_8 being ethoxyethyl is shown below:



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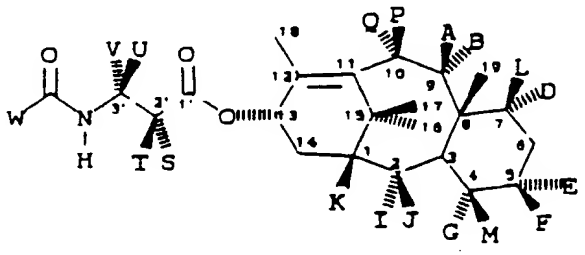
According to IUPAC rules, the name of oxazinone 2 is 2,4-diphenyl-5-(1-ethoxyethoxy)-4,5-dihydro-1,3-oxazin-6-one.

In accordance with the present invention, a process is provided for preparing taxol intermediates, natural taxol and non-naturally occurring taxols having the following structural formula:



3

wherein

A and B are independently hydrogen or lower alkanoyloxy, alkenoyloxy, alkynoyloxy, or aryloyloxy or
A and B together form an oxo;
L and D are independently hydrogen or hydroxy or lower alkanoyloxy, alkenoyloxy, alkynoyloxy, or aryloyloxy;
E and F are independently hydrogen or lower alkanoyloxy, alkenoyloxy, alkynoyloxy, or aryloyloxy or;
E and F together form an oxo;
G is hydrogen or hydroxy or lower alkanoyloxy, alkenoyloxy, alkynoyloxy, or aryloyloxy or
G and M together form an oxo or methylene or
G and M together form an oxirane ring or
M and F together form an oxetane ring;
J is hydrogen, hydroxy, or lower alkanoyloxy, alkenoyloxy, alkynoyloxy, or aryloyloxy or
I is hydrogen, hydroxy, or lower alkanoyloxy, alkenoyloxy, alkynoyloxy, or aryloyloxy; or
I and J taken together form an oxo; and
K is hydrogen, hydroxy or lower alkoxy, alkanoyloxy, alkenoyloxy, alkynoyloxy, or aryloyloxy; and
P and Q are independently hydrogen or lower alkanoyloxy, alkenoyloxy, alkynoyloxy, or aryloyloxy or
P and Q together form an oxo; and
S and T are independently hydrogen or lower alkanoyloxy, alkenoyloxy, alkynoyloxy, or aryloyloxy or
S and T together form an oxo; and
U and V are independently hydrogen or lower alkyl, alkenyl, alkynyl, aryl, or substituted aryl; and
W is aryl, substituted aryl, lower alkyl, alkenyl, or alkynyl.

The taxol alkyl groups, either alone or with the various substituents defined hereinabove are preferably lower alkyl containing from one to six carbon atoms in the principal chain and up to 10 carbon atoms. They may be straight or branched chain and include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, aryl, hexyl, and the like.

The taxol alkenyl groups, either alone or with the various substituents defined hereinabove are preferably lower alkenyl containing from two to six carbon atoms in the principal chain and up to 10 carbon atoms. They may be straight or branched chain and include ethenyl, propenyl, isopropenyl, butenyl, isobutenyl, aryl, hexenyl, and the like.

The taxol alkynyl groups, either alone or with the various substituents defined hereinabove are preferably lower alkynyl containing from two to six carbon atoms in the principal chain and up to 10 carbon atoms. They may be straight or branched chain and include ethynyl, propynyl, butynyl, isobutynyl, hexynyl, and the like.

Exemplary alkanoyloxy include acetate, propionate, butyrate, valerate, isobutyrate and the like. The more preferred alkanoyloxy is acetate.

The taxol aryl moieties, either alone or with various substituents contain from 6 to 10 carbon atoms and include phenyl, α-naphthyl and β-naphthyl. Substituents include alkanoxy, hydroxy, halogen, alkyl, aryl, alkenyl, acyl, acyloxy, nitro, amino, and amido. Phenyl is the more preferred aryl.

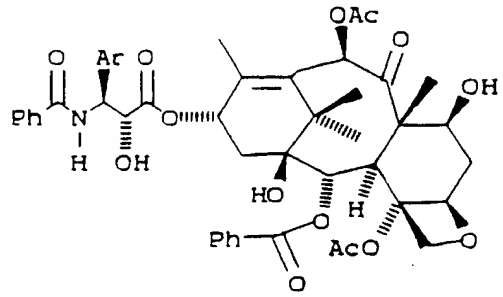
As defined herein, the term "aryloyloxy" includes aromatic heterocyclic moieties the term "aryl" includes any compound having an aromatic ring of which no hetero atom is a member, and the term "heteroaryl" includes any compound having an aromatic ring which comprises a hetero atom.

Preferred values of the substituents A, B, D, L, E, F, G, M, I, J, K, P, Q, S, T, U, V, and W are enumerated below in Table I.

Table I

A and B together, form an oxo	A=H B=OAc,	A=OCOR B=H,	A=B=H;		
L=H D=OH,	L=OH D=H,	L=D=H;			
E=H, F=OAc,	E=OAc, F=H	E and F together form an oxo,	E=H F=O (oxetane);		
G and M=CH_2,	G=CH_2 M=O (epoxide)	G=O M=CH_2 (epoxide),	G and M together form an oxo,	G=OAc M=CH_2O (oxetane);	G=H M=CH_2O (oxetane);
I=J=O,	I=J=H	I=COPh J=H;	I=COAr J=H;		
K=H,	K=OH,	K=OR,	K=OCOR,	K=OCOAr,	
P and Q together, form an oxo	P=H Q=OAc,	P=OCOR Q=H,	P=Q=H;		
S and T together, form an oxo	S=H T-OCOR,	S=H T=OR,	S=OCOR T=H,	S=OR T=H,	S=OH T=H, S=H T=OH;
U=H V=R,	U=H V=Ph,	U=H V=Ar,	U=Ph V=H,	U=Ar V=H,	U=R V=H, U=V=H;
W=R,	W=Ph,	W=Ar;			

Exemplary compounds within the generic formula are depicted hereinbelow:



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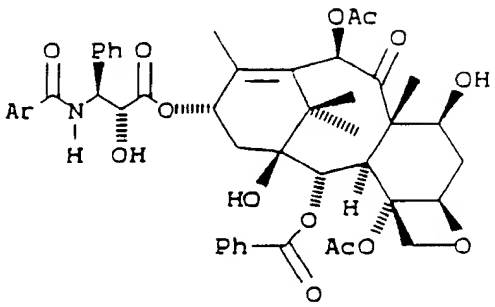

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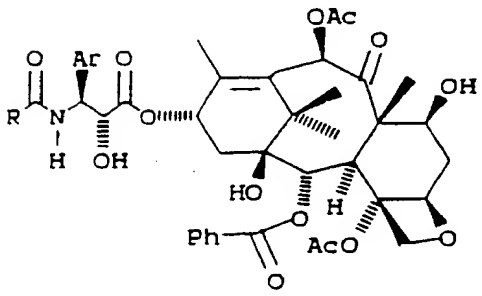

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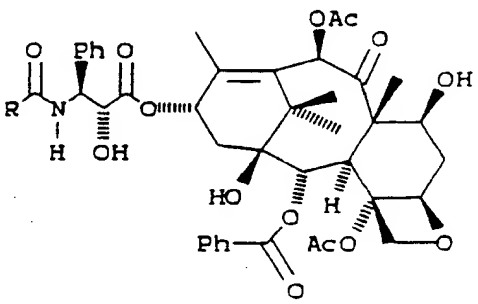

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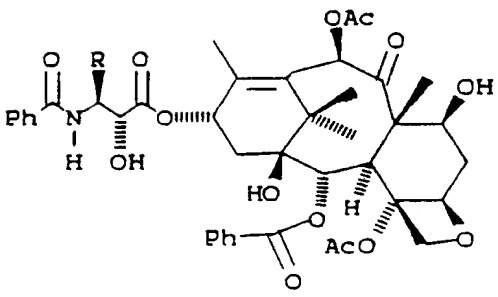

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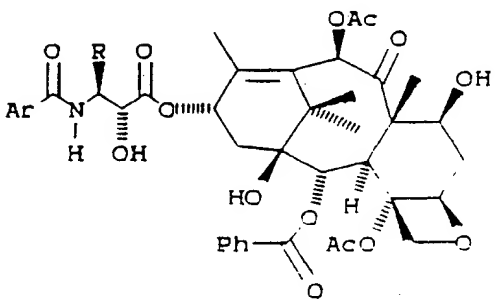

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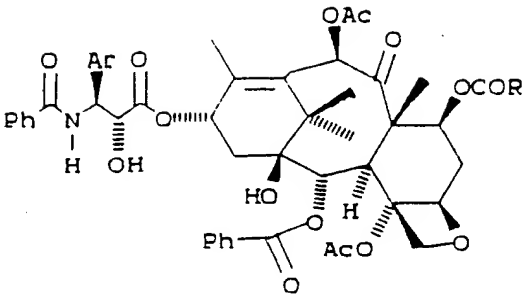

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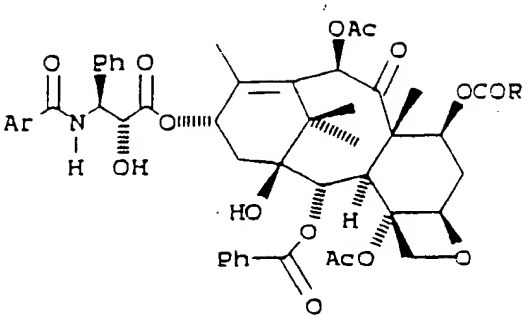

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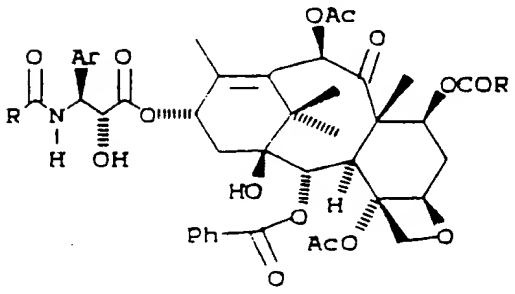

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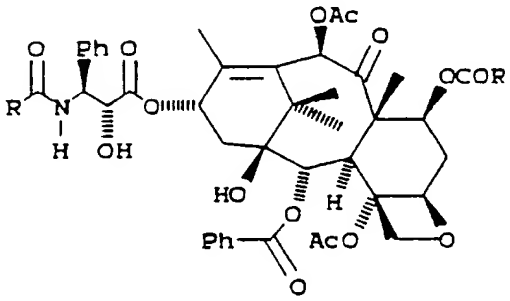

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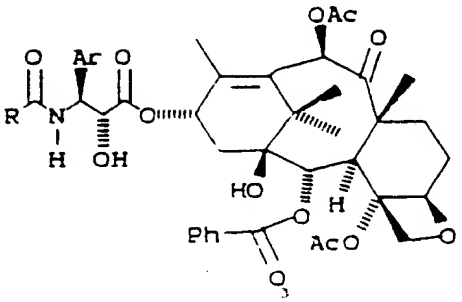

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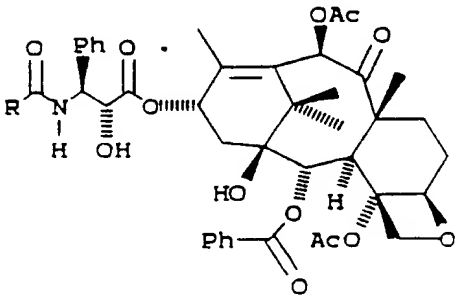

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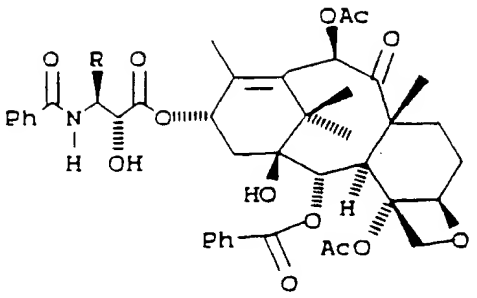

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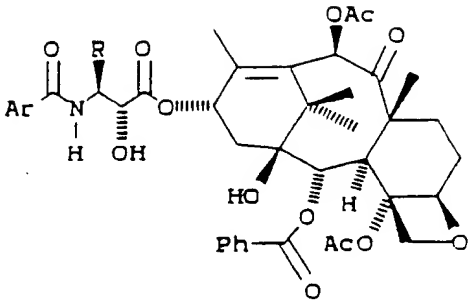

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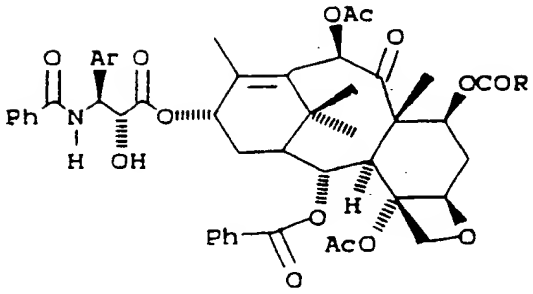

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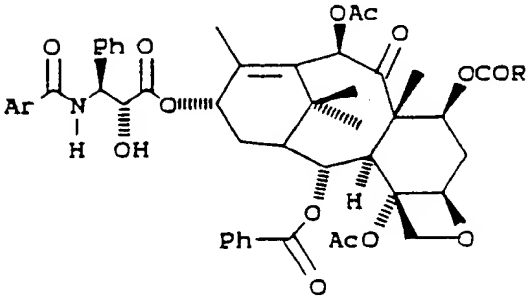

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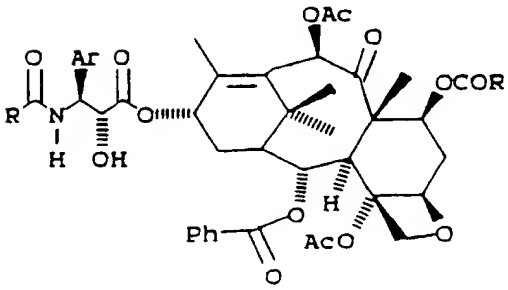

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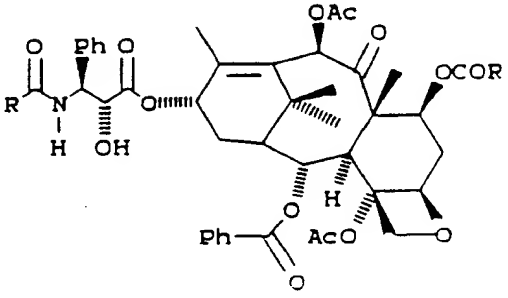

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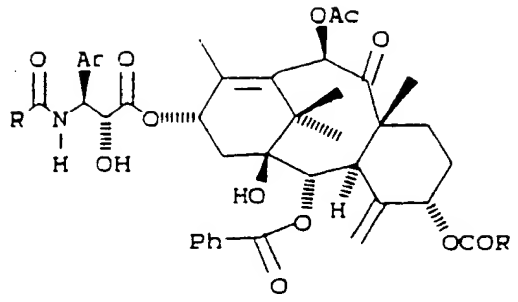

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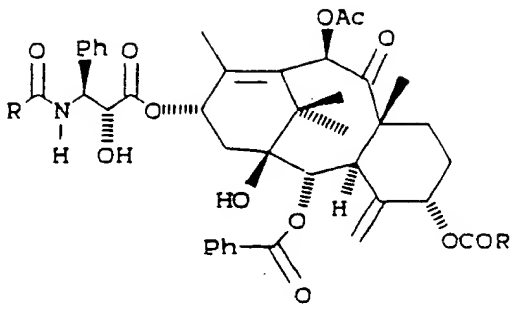

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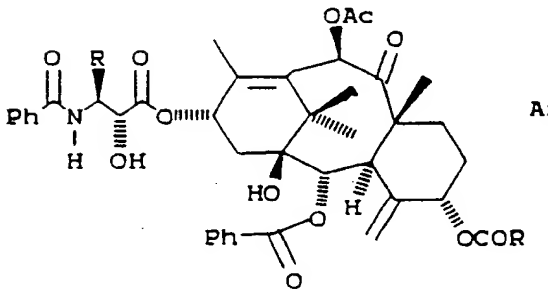

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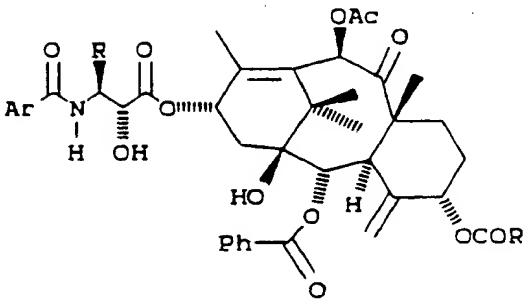

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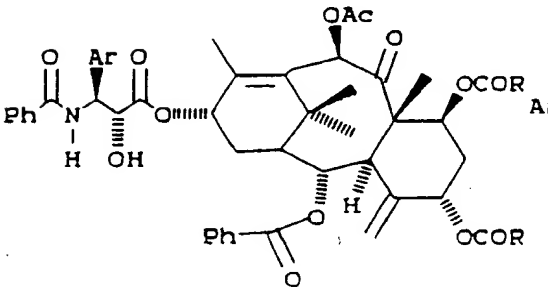

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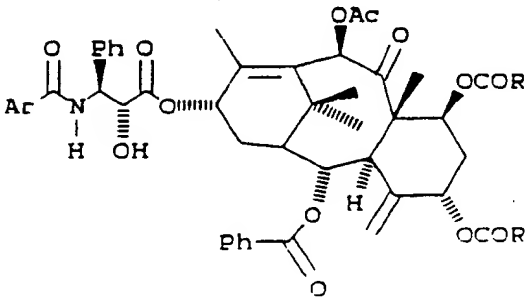

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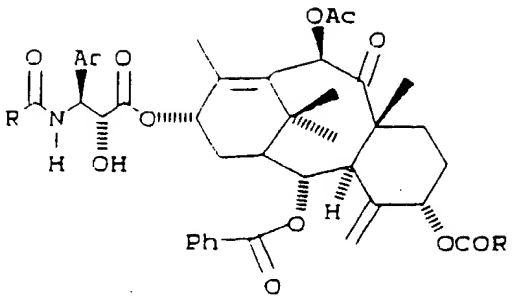

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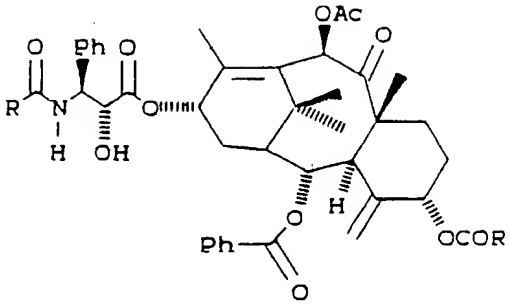
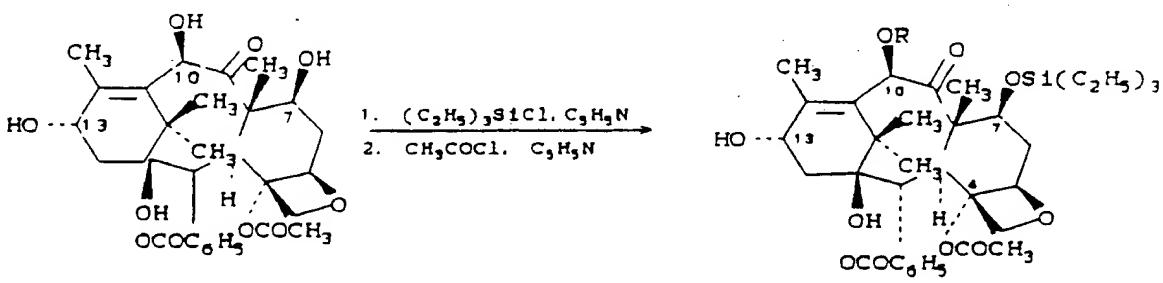


29

In accordance with the process of the present invention, oxazinones **1** are converted to β-amido esters Sin the presence of an alcohol and an activating agent, preferably a tertiary amine such as triethyl amine, diisopropyl ethyl amine, pyridine, N-methyl imidazole, and 4-dimethylaminopyridine (DMAP). For example, oxazinones **1** react with compounds having the taxane tetracyclic nucleus and a C13 hydroxyl group, in the presence of 4-dimethyl- aminopyridine (DMAP), to provide substances having a β-amido ester group at C13.

Most preferably, the alcohol is 7-O-triethylsilyl baccatin III which can be obtained as described by Greene, et al. in JACS 110, 5917 (1988) or by other routes. As reported in Greene et al., 10-deacetyl baccatin III is converted to 7-O-triethylsilyl baccatin III according to the following reaction scheme:



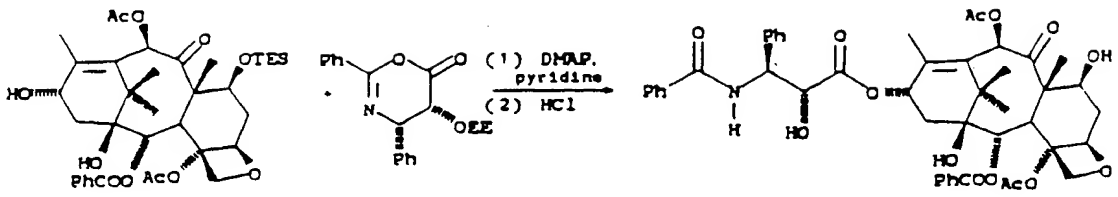
30

31 a, R=H
b, R=$COCH_3$

Under what is reported to be carefully optimized conditions, 10-deacetyl baccatin III is reacted with 20 equivalents of $(C_2H_5)_3SiCl$ at 23°C under an argon atmosphere for 20 hours in the presence of 50 mL of pyridine/mmol of 10-deacetyl baccatin III to provide 7-triethylsilyl-10-deacetyl baccatin III (**31a**) as a reaction product in 84-86% yield after purification. The reaction product is then acetylated with 5 equivalents of CH_3COCl and 25 mL of pyridine/mmol of **31a** at 0 °C under an argon atmosphere for 48 hours to provide 86% yield of 7-O-triethylsilyl baccatin III (**31b**). Greene, et al. in JACS 110, 5917 at 5918 (1988).

As shown in the following reaction scheme, 7-O-triethylsilyl baccatin III **31b** may be reacted with an oxazinone of the present invention at room temperature to provide a taxol intermediate in which the C-7 and C-2′ hydroxyl groups are protected with triethylsilyl and ethoxyethyl protecting groups, respectively. These groups are then hydrolyzed under mild conditions so as not to disturb the ester linkage or the taxol substituents. The synthesis of taxol from oxazinone **2** is

carried out as follows:



31b 2 TAXOL

Although the present scheme is directed to the synthesis of the natural product taxol, it can be used with modifications in either the oxazinone or the tetracyclic alcohol, which can be derived from natural or unnatural sources, to prepare other synthetic taxols contemplated within the present invention.

Alternatively, an oxazinone **1** may be converted to a β-amido ester in the presence of an activating agent and an alcohol other than 7-O-triethylsilyl baccatin III to form a taxol intermediate. Synthesis of taxol may then proceed using the taxol intermediate under an appropriate reaction scheme.

The oxazinone alkyl groups, either alone or with the various substituents defined hereinabove are preferably lower alkyl containing from one to six carbon atoms in the principal chain and up to 15 carbon atoms. They may be straight or branched chain and include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, amyl, hexyl, and the like.

The oxazinone alkenyl groups, either alone or with the various substituents defined hereinabove are preferably lower alkenyl containing from two to six carbon atoms in the principal chain and up to 15 carbon atoms. They may be straight or branched chain and include ethenyl, propenyl, isopropenyl, butenyl, isobutenyl, amyl, hexenyl, and the like.

The oxazinone alkynyl groups, either alone or with the various substituents defined hereinabove are preferably lower alkynyl containing from two to six carbon atoms in the principal chain and up to 15 carbon atoms. They may be straight or branched chain and include ethynyl, propynyl, butynyl, isobutynyl, aryl, hexynyl, and the like.

Exemplary oxazinone alkanoyloxy include acetate, propionate, butyrate, valarate, isobutyrate and the like. The more preferred alkanoyloxy is acetate.

The oxazinone aryl moieties described, either alone or with various substituents contain from 6 to 15 carbon atoms and include phenyl, α-naphthyl or β-naphthyl, etc. Substituents include alkanoxy, hydroxy, halogen, alkyl, aryl, alkenyl, acyl, acyloxy, nitro, amino, amido, etc. Phenyl is the more preferred aryl.

As noted above, R_2 and R_5 of oxazinone **1** may be OR_8 with R_8 being alkyl, acyl, ketal, ethoxyethyl ("EE"), 2,2,2-trichloroethoxymethyl, or other hydroxyl protecting group such as acetals and ethers, i.e., methoxymethyl ("MOM"), benzyloxymethyl; esters, such as acetates; carbonates, such as methyl carbonates; and the like. A variety of protecting groups for the hydroxyl group and the synthesis thereof may be found in "Protective Groups in Organic Synthesis" by T. W. Greene, John Wiley and Sons, 1981. The hydroxyl protecting group selected should be easily removed under conditions that are sufficiently mild so as not to disturb the ester linkage or other substituents of the taxol intermediate. However, R_8 is preferably ethoxyethyl or 2,2,2-trichloroethoxymethyl, and most preferably ethoxyethyl.

Preferred values of the oxazinone substituents R_1, R_2, R_3, R_5, R_6, R_7, and R_8 are enumerated herein below:

R_1=OR_7 R_2=OR_8 R_3=Ph R_5=H R_6=H

R_1=Ar
- R_1=p-MeOPh
- R_1=alkyl
- R_1=alkenyl
- R_1=alkynyl
- R_1=H

R_3=Ar
- R_3=p-MeOPh
- R_3=alkyl
- R_3=alkenyl
- R_3=alkynyl
- R_3=H

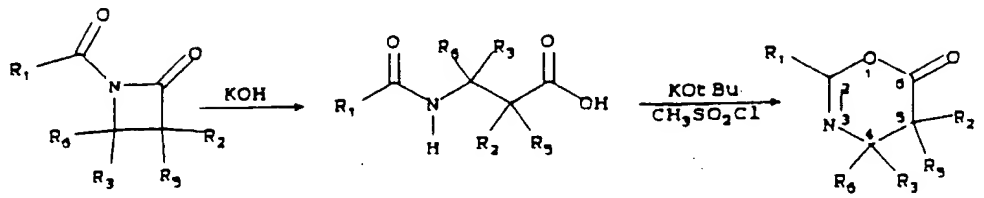
R_7=alkyl
- R_7=alkenyl
- R_8=alkyl
- R_8=EE

R_7=alkenyl
- R_7=alkynyl
- R_8=OCOR
- R_8=MOM

R_7=aryl
- R_7=heteroaryl
- R_8=$Cl_3CCH_2OCH_2$

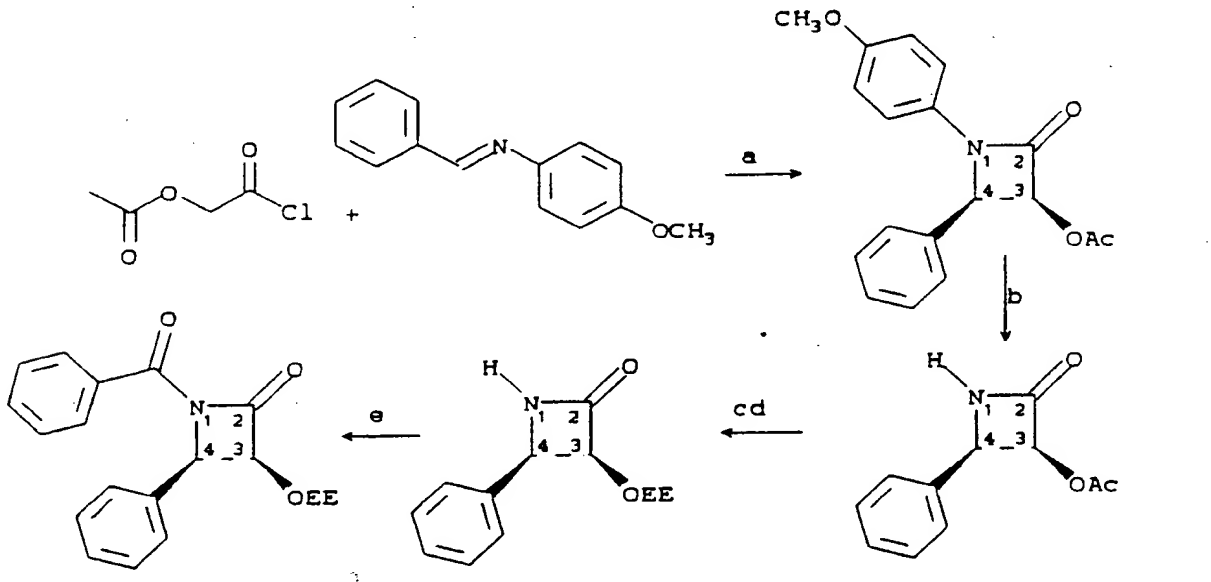
Since the oxazinone **1** has several asymmetric carbons, it is known to those skilled in the art that the compounds of the present invention having asymmetric carbon atoms may exist in diastereomeric, racemic, or optically active forms. All of these forms are contemplated within the scope of this invention. More specifically, the present invention includes enantiomers, diastereomers, racemic mixtures, and other mixtures thereof.

The oxazinones **1** can be prepared from readily available materials according to the following reaction scheme:



32 **33** **1**

Carboxylic acid **33** may alternatively be prepared according to the method described in Greene et al., JACS 110, 5917 (1988). β-lactams **32** can be prepared from readily available materials, as illustrated in the following reaction scheme in which R_1 and R_3 are phenyl, R_5 and R_6 are hydrogen and R_2 is OR_8 with R_8 being ethoxyethyl:



reagents: (a) triethylamine, CH_2Cl_2, 25°C, 18h; (b) 4 equiv ceric ammonium nitrate, CH_3CN, -10 °C, 10 min; (c) KOH, THF, H_2O, O °C, 30 min; (d) ethyl vinyl ether, THF, toluene sulfonic acid (cat.), O °C, 1.5h; (e) CH_3Li, ether, -78 °C, 10 min; benzoyl chloride, -78 °C, 1h.

The starting materials are readily available. α-Acyloxy acetyl chloride is prepared from glycolic acid, and, in the presence of a tertiary amine, it cyclocondenses with imines prepared from aldehydes and p-methoxyaniline to give 1-p-methoxyphenyl-3-acyloxy-4-arylazetidin-2-ones.

The p-methoxyphenyl group can be readily removed through oxidation with ceric ammonium nitrate, and the acyloxy group can be hydrolyzed under standard conditions familiar to those experienced in the art to provide 3-hydroxy-4-arylazetidin-2-ones.

The 3-hydroxyl group may be protected with a variety of standard protecting groups such as the 1-ethoxyethyl group. Preferably, the racemic 3-hydroxy-4-arylazetidin-2-one is resolved into the pure enantiomers prior to protection by recrystallization of the corresponding 2-methoxy-2-(trifluoromethyl) phenylacetic esters and only the dextrorotatory enantiomer

is used in the preparation of taxol. In any event, the 3-(1-ethoxyethoxy)-4-phenylazetidin-2-one can be converted to β-lactam **32**, by treatment with a base, preferably n-butyllithium, and an aroyl chloride at -78 °C or below.

The following examples illustrate the invention.

EXAMPLE 1

PREPARATION OF CIS-2,4-DIPHENYL-5-(1-ETHOXYETHOXY)-4,5-DIHYDRO-1,3-OXAZIN-6-ONE 2

cis-1-p-methoxyphenyl-3-acetoxy-4-phenylazetidin-2-one. To a solution of 962 mg (4.56 mmol) of the imine derived from benzaldehyde and p-methoxy aniline, and 0.85 mL (6.07 mmol) of triethylamine in 15 mL of CH_2Cl_2 at -20°C was added dropwise a solution of 413 mg (3.04 mmol) of α-acetoxy acetyl chloride in 15 mL of CH_2Cl_2. The reaction mixture was allowed to warm to 25°C over an 18 h period. The reaction mixture was then diluted with 100 mL of CH_2Cl_2 and the solution was extracted with 30 mL of 10% aqueous HCl. The organic layer was washed with 30 mL of water and 30 mL of saturated aqueous sodium bicarbonate, dried over sodium sulfate, and concentrated to provide a solid mass. The solid was triturated with 50 mL of hexane and the mixture was filtered. The remaining solid was recrystallized from ethyl acetate/hexane to give 645 mg (68%) of cis-1-p-methoxyphenyl-3-acetoxy-4-phenylazetidin-2-one as white crystals, m.p. 163°C.

cis-3-acetoxy-4-phenylazetidin-2-one. To a solution of 20.2 g of cis-1-p-methoxyphenyl-3-acetoxy-4-phenylazetidin-2-one in 700 mL of acetonitrile at -10°C was slowly added a solution of ceric ammonium nitrate in 450 mL of water over a 1 h period. The mixture was stirred for 30 min at -10°C and diluted with 500 mL of ether. The aqueous layer was extracted with two 100 mL portions of ether, and the combined organic layer was washed with two 100 mL portions of water, two 100 mL portions of saturated aqueous sodium bisulfite, two 100 mL portions of saturated aqueous sodium bicarbonate and concentrated to give 18.5 g of a solid. Recrystallization of the solid from acetone/hexane gave 12.3 g (92%) of cis-3-acetoxy-4-phenylazetidin-2-one as white crystals, m.p. 152-154°C.

cis-3-hydroxy-4-phenylazetidin-2-one. To a mixture of 200 mL of THF and 280 mL of 1 M aqueous potassium hydroxide solution at 0°C was added a solution of 4.59 g (22.4 mmol) of cis-3-acetoxy-4-phenylazetidin-2-one in 265 mL of THF via a dropping funnel over a 40 min period. The solution was stirred at 0°C for 1 h and 100 mL of water and 100 mL of saturated sodium bicarbonate were added. The mixture was extracted with four 200 mL portions of ethyl acetate and the combined organic layers were dried over sodium sulfate and concentrated to give 3.54 g (97%) of racemic cis-3-hydroxy-4-phenylazetidin-2-one as white crystals, m.p. 147-149°C. This material was resolved into its enantiomers by recrystallisation of its 2-methoxy-2-(trifluoromethyl)phenylacetic ester from hexane/acetone followed by hydrolysis $[\alpha]^{25}_{Hg}$177°.

cis-3-(1-ethoxyethoxy)-4-phenylazetidin-2-one. To a solution of 3.41 g (20.9 mmol) of cis-3-hydroxy-4-phenylazetidin-2-one in 15 mL of THF at 0°C was added 5 mL of ethyl vinyl ether and 20 mg (0.2 mmol) of methanesulfonic acid. The mixture was stirred at 0°C for 20 min, diluted with 20 mL of saturated aqueous sodium bicarbonate, and extracted with three 40 mL portions of ethyl acetate. The combined ethyl acetate layers wre dried over sodium sulfate and concentrated to give 4.87 g (99%) of cis-3-(1-ethoxyethoxy)-4-phenylazetidin-2-one as a colorless oil.

cis-1-benzoyl-3-(1-ethoxyethoxy)-4-phenylazetidin-2-one. To a solution of 2.35 g (10 mmol) of cis-3-(1-ethoxyethoxy)-4-phenylazetidin-2-one in 40 mL of THF at -78°C was added 6.1 mL (10.07 mmol) of a 1.65 M solution of n-butyllithium in hexane. The mixture was stirred for 10 min at -78°C and a solution of 1.42 g (10.1 mmol) of benzoyl chloride in 10 mL of THF was added. The mixture was stirred at -78°C for 1 h and diluted with 70 mL of saturated aqueous sodium bicarbonate and extracted with three 50 mL portions of ethyl acetate. The combined ethyl acetate extracts were dried over sodium sulfate and concentrated to give 3.45 g of an oil. Chromatography of the oil on silica gel eluted with ethyl acetate/hexane gave 3.22 g (95%) of cis-1-benzoyl-3-(1-ethoxyethoxy)-4-phenylazetidin-2-one as a colorless oil.

2R,3S-N-benzoyl-O-(1-ethoxyethyl)-3-phenylisoserine. To a solution of 460 mg (1.36 mmol) of cis-1-benzoyl-3-(1-ethoxyethoxy)-4-phenylazetidin-2-one in 20 mL of THF at 0°C was added 13.5 mL of a 1M aqueous solution (13.5 mmol) of potassium hydroxide. The mixture was stirred at 0°C for 10 min and the THF was evaporated. The mixture was partitioned between 12 mL of a 1N aqueous HCl solution and 30 mL of chloroform. The aqueous layer was extracted with two additional 30 mL portions of chloroform. The combined chloroform extracts were dried over sodium sulfate and concentrated to provide 416 mg (86%) of 2R,3S-N-benzoyl-O-(1-ethoxyethyl)-3-phenylisoserine (formula **33** in which R_1 and R_3 are phenyl and R_2 is ethoxyethyl).

cis-2,4-diphenyl-5-(1-ethoxyethoxy)-4,5-dihydro-1,3-oxazin-6-one 2. To a solution of 416 mg (1.16 mmol) of 2R,3S-N-benzoyl-O-(1-ethoxyethyl)-3-phenylisoserine in 20 mL of THF was added 261 mg (2.33 mmol) of solid potassium tert-butoxide and the mixture was stirred at 25°C for 30 min. A solution of 134 mg (1.16 mmol) of methanesulfonyl chloride in 3.2 mL of THF was added and the mixture was stirred at 25°C for 1.5 h. The mixture was diluted with 80 mL of hexane and ethyl acetate and this solution was extracted with 20 mL of saturated aqueous sodium bicarbonate solution and 10 mL of brine. The organic phase was dried over sodium sulfate and concentrated to give 256 mg (65%) of cis-2,4-diphenyl-5-(1-ethoxyethoxy)-4,5-dihydro-1,3-oxazin-6-one **2** as a colorless oil, $[\alpha]^{25}_{Hg}$ -22° ($CHCl_3$, c 1.55).

EXAMPLE 2

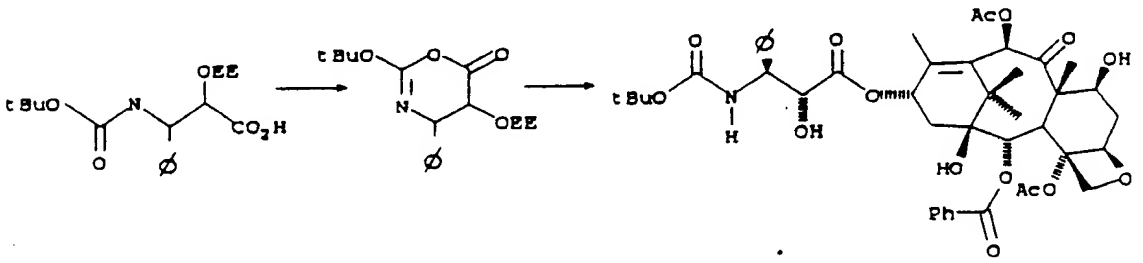
PREPARATION OF TAXOL

To a small reaction vessel was added 77 mg (0.218 mmol) of (-)-cis-2,4-diphenyl-5-(1-ethoxyethoxy)-4,5-dihydro-1,3-oxazin-6-one **2**, 40 mg (0.057 mmol) of 7-O-triethylsilyl baccatin III, 6.9 mg (0.057 mmol) of 4-dimethylamino pyridine (DMAP), and 0.029 mL of pyridine. The mixture was stirred at 25°C for 12 h and diluted with 100 mL of ethyl acetate. The ethyl acetate solution extracted with 20 mL of 10% aqueous copper sulfate solution, dried over sodium sulfate and concentrated. The residue was filtered through a plug of silica gel eluted with ethyl acetate. Flash chromatography on silica gel eluted with ethyl acetate/hexane followed by recrystallization from ethyl acetate/hexane gave 46 mg (77%) of 2′-O-(1-ethoxyethyl)-7-O-triethylsilyl taxol as a ca. 2:1 mixture of diastereomers and 9.3 mg (23%) of 7-O-triethylsilyl baccatin III. The yield based on consumed 7-O-triethylsilyl baccatin III was quantitative.

A 5 mg sample of 2′-(1-ethoxyethyl)-7-O-triethylsilyl taxol was dissolved in 2 mL of ethanol and 0.5 mL of 0.5% aqueous HCl solution was added. The mixture was stirred at 0°C for 30 h and diluted with 50 mL of ethyl acetate. The solution was extracted with 20 mL of saturated aqueous sodium bicarbonate solution, dried over sodium sulfate and concentrated. The residue was purified by column chromatography on silica gel eluted with ethyl acetate/hexane to provide 3.8 mg (ca. 90%) of taxol, which was identical with an authentic sample in all respects.

EXAMPLE 3

PREPARATION OF N-DEBENZOYL-N-TERTBUTOXYCARBONYL TAXOL



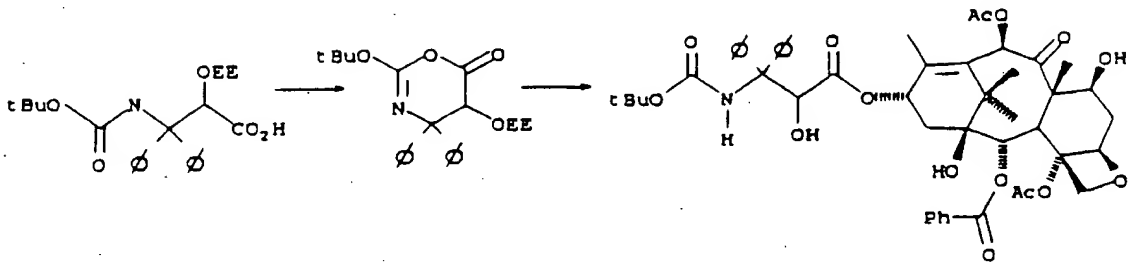
2-tertbutoxy-4-phenyl-5-(1-ethoxyethoxy)-4,5-dihydro-1,3-oxazin-6-one. To a solution of 409 mg (1.16 mmol) of N-tertbutoxycarbonyl-O-(1-ethoxyethyl)-3-phenylisoserine (3) in 20 mL of THF is added 261 mg (2.33 mmol) of solid potassium tert-butoxide and the mixture is stirred at 25°C for 30 min. A solution of 134 mg (1.16 mmol) of methanesulfonyl chloride in 3.2 mL of THF is added and the mixture is stirred at 25°C for 1.5 hour. The mixture is diluted with 80 mL of hexane an ethyl acetate and this ssolution is extracted with 20 mL of saturated aqueous sodium bicarbonate solution and 10 mL of brine. The organic phase is dried over sodium sulfate and concentrated to give 235 mg (70%) of 2-tertbutoxy-4-phenyl-5-(1-ethoxyethoxy)-4,5-dihydro-1,3-oxazin-6-one as a colorless oil.

N-debenzoyl-N-tertbutoxycarbonyl taxol. To a small reaction vessel is added 73 mg (0.218 mmol) of 2-tertbutoxy-4-phenyl-5-(1-ethoxyethoxy)-4,5-dihydro-1,3-oxazin-6-one, 40 mg (0.057 mmol) of 7-O-triethylsilyl baccatin III, 6.9 mg (0.057 mmol) of 4-dimethylamino pyridine (DMAP), and 0.029 mL of pyridine. The mixture is stirred at 25°C for 12 hours and diluted with 100 mL of ethyl acetate. The ethyl acetate solution is extracted with 20 mL of 10% aqueous copper sulfate solution, dried over sodium sulfate and concentrated. The residue is filtered through a plug of silica gel eluted with ethyl acetate. Flash chromatography on silica gel eluted with ethyl acetate/hexane followed by recrystallization from ethyl acetate/hexane gives 44 mg (73%) of N-debenzoyl-N-tertbutoxycarbonyl-2′-(1-ethoxyethoxy)-7-O-triethylsilyl taxol as a ca. 1:1 mixture of diastereomers and 9.3 mg (23%) of 7-O-triethylsilyl baccatin III.

A 5 mg sample of N-debenzoyl-N-tertbutoxycarbonyl-2′-(1-ethoxyethoxy)-7-O-triethylsilyl taxol is dissolved in 2 mL of ethanol and 0.5 mL of 0.5% aqueous HCl solution is added. The mixture is stirred at 0°C for 30 hours and diluted with 50 mL of ethyl acetate. The solution is extracted with 20 mL of saturated aqueous sodium bicarbonate solution, dried over sodium sulfate and concentrated. The residue is purified by column chromatography on silica gel eluted with ethyl acetate/hexane to provide 3.8 mg (ca. 90%) of N-debenzoyl-N-tertbutoxycarbonyl taxol.

EXAMPLE 4

PREPARATION OF N-DEBENZOYL-N-TERTBUTOXYCARBONYL-2′-(1-ETHOXYETHYL)-3′-PHENYL-TAXOL



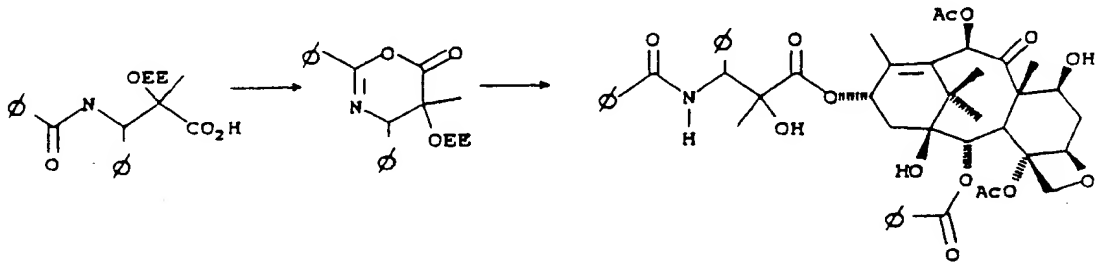
2-tertbutoxy-4,4-diphenyl-5-(1-ethoxyethoxy)-4,5-dihydro-1,3-oxazin-6-one. To a solution of 497 mg (1.16 mmol) of N-tertbutoxycarbonyl-O-(1-ethoxyethyl)-3,3-diphenylisoserine (3) in 20 mL of THF is added 261 mg (2.33 mmol) of solid potassium tert-butoxide and the mixture is stirred at 25°C for 30 min. A solution of 134 mg (1.16 mmol) of methanesulfonyl chloride in 3.2 mL of THF is added and the mixture is stirred at 25°C for 1.5 hour. The mixture is diluted with 80 mL of hexane and ethyl acetate, and this solution is extracted with 20 mL of saturated aqueous sodium bicarbonate solution and 10 mL of brine. The organic phase is dried over sodium sulfate and concentrated to give 243 mg (59%) of 2-tertbutoxy-4,4-diphenyl-5-(1-ethoxyethoxy)-4,5-dihydro-1,3-oxazin-6-one as a colorless oil.

N-debenzoyl-N-tertbutoxycarbonyl-3′-phenyl taxol. To a small reaction vessel is added 90 mg (0.218 mmol) of 2-tertbutoxy-4,4-diphenyl-5-(1-ethoxyethoxy)-4,5-dihydro-1,3-oxazin-6-one, 40 mg (0.057 mmol) of 7-O-triethylsilyl baccatin III, 6.9 mg (0.057 mmol) of 4-dimethylamino pyridine (DMAP), and 0.029 mL of pyridine. The mixture is stirred at 25°C for 12 hours and diluted with 100 mL of ethyl acetate. The ethyl acetate solution is extracted with 20 mL of 10% aqueous copper sulfate solution, dried over sodium sulfate and concentrated. The residue is filtered through a plug of silica gel eluted with ethyl acetate. Flash chromatography on silica gel eluted with ethyl acetate/hexane followed by recrystallization from ethyl acetate/hexane gives 44 mg (66%) of N-debenzoyl-N-tertbutoxycarbonyl-2′-(1-ethoxyethyl)3′-phenyl-7-O-triethylsilyl taxol as a ca. 3:1 mixture of diastereomers.

A 5 mg sample of N-debenzoyl-N-tertbutoxycarbonyl-2'-(1-ethoxyethyl)3′-phenyl-7-O-triethylsilyl taxol is dissolved in 2 mL of ethanol and 0.5 mL of 0.5% aqueous HCl solution is added. The mixture is stirred at 0°C for 30 hours and diluted with 50 mL of ethyl acetate. The solution is extracted with 20 mL of saturated aqueous sodium bicarbonate solution, dried over sodium sulfate and concentrated. The residue is purified by column chromatography on silica gel eluted with ethyl acetate/hexane to provide 4.0 mg (ca. 90%) of N-debenzoyl-N-tertbutoxycarbonyl-3′-phenyl taxol.

EXAMPLE 5

PREPARATION OF 2,4-DIPHENYL-5-(1-ETHOXYETHOXY)-5-METHYL-4,5-DIHYDRO-1,3-OXAZIN-6-ONE



To a solution of 430 mg (1.16 mmol) of N-benzoyl-O-(1-ethoxyethyl)-2-methyl-3-phenylisoserine in 20 mL of THF is added 261 mg (2.33 mmol) of solid potassium tert-butoxide and the mixture is stirred at 25°C for 30 min. A solution of 134 mg (1.16 mmol) of methanesulfonyl chloride in 3.2 mL of THF is added and the mixture is stirred at 25°C for 1.5 hour. The mixture is diluted with 80 mL of hexane and ethyl acetate and this solution is extracted with 20 mL of saturated aqueous sodium bicarbonate solution and 10 mL of brine. The organic phase is dried over sodium sulfate and is concentrated to give 270 mg (76%) of 2,4-diphenyl-5-(1-ethoxyethoxy)-5-methyl-4,5-dihydro-1,3-oxazin-6-one as a colorless oil.

EXAMPLE 6

3′-METHYL TAXOL

To a small reaction vessel is added 77 mg (0.218 mmol) of 2,4-diphenyl-5-(1-ethoxyethoxy)-5-methyl-4,5-dihydro-1,3-oxazin-6-one, 40 mg (0.057 mmol) of 7-O-triethylsilyl baccatin III, 6.9 mg (0.057 mmol) of 4-dimethylamino pyridine (DMAP), and 0.029 mL of pyridine. The mixture is stirred at 25°C for 12 hours and diluted with 100 mL of ethyl acetate. The ethyl acetate solution is extracted with 20 mL of 10% aqueous copper sulfate solution, dried over sodium sulfate and concentrated. The residue is filtered through a plug of silica gel eluted with ethyl acetate. Flash chromatography on silica gel eluted with ethyl acetate/hexane followed by recrystallisation from ethyl acetate/hexane gives 32 mg (53%) of 2′-(1-ethoxy- ethyl)-3′-methyl-7-O-triethylsilyl taxol as a ca. 1:1 mixture of diastereomers.

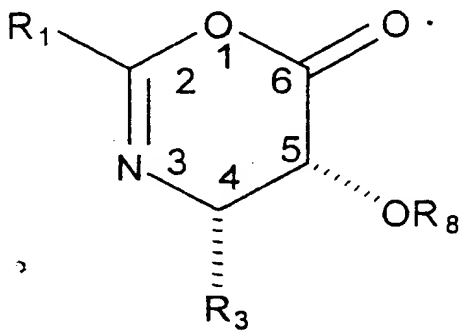
A 5 mg sample of 2′-(1-ethoxyethyl)-3′-methyl-7-O-triethylsilyl taxol is dissolved in 2 mL of ethanol and 0.5 mL of 0.5% aqueous HCl solution is added. The mixture is stirred at 0°C for 30 hours and diluted with 50 mL of ethyl acetate. The solution is extracted with 20 mL of saturated aqueous sodium bicarbonate solution, dried over sodium sulfate and concentrated. The residue is purified by column chromatography on silica gel eluted with ethyl acetate/hexane to provide 3.9 mg (ca. 90%) of 3′-methyl taxol.

In view of the above, it will be seen that the several objects of the invention are achieved.

As various changes could be made in the above compositions and processes without departing from the scope of the invention, it is intended that all matter contained in the above description be interpreted as illustrative and not in a limiting sense.

Claims

1. An oxazinone of the formula:



wherein R_1 is C_{6-15} aryl, substituted C_{6-15} aryl, heteroaryl, C_{1-15} alkyl, C_{2-15} alkenyl, C_{2-15} alkynyl, or OR_7 wherein R_7 is C_{1-15} alkyl, C_{2-15} alkenyl, C_{2-15} alkynyl, C_{6-15} aryl or heteroaryl; R_8 is ethoxyethyl, 2,2,2-trichloroethoxymethyl or other hydroxyl protecting group; and R_3 is hydrogen, C_{1-15} alkyl, C_{2-15} alkenyl, C_{2-15} alkynyl, C_{6-15} aryl, substituted C_{6-15} aryl, and heteroaryl; and wherein substituted C_{6-15} aryl means C_{6-15} aryl substituted by at least one substituent selected from alkanoxy, hydroxy, halogen, alkyl, aryl, alkenyl, acyl, acyloxy, nitro, and amido.

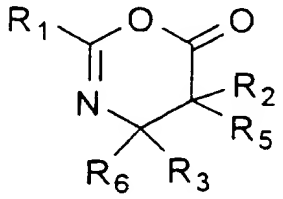
2. An oxazinone according to claim 1, wherein the hydroxyl protecting group is selected from the group consisting of acetals, ethers, esters, and carbonates.

3. An oxazinone according to claim 1 or claim 2, wherein R_1 is aryl; R_8 is ethoxyethyl, or 2,2,2-trichloroethoxymethyl; and R_3 is C_{6-15} aryl.

4. An oxazinone according to any one of claims 1 to 3, wherein R_1 and R_3 are phenyl.

5. The enantiomers and diastereomers of an oxazinone according to any one of claims 1 to 4.

6. A process for the preparation of a taxol intermediate comprising contacting an alcohol having the taxane tetracyclic nucleus and a C-13 hydroxyl group with an oxazinone having the formula:

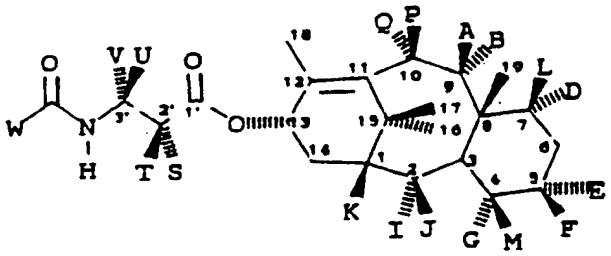


wherein R_1 and R_3 are as defined in claim 1; R_2 and R_5 are independently selected from hydrogen, C_{1-15} alkyl, C_{2-15} alkenyl, C_{2-15} alkynyl, C_{6-15} aryl, substituted C_{6-15} aryl, heteroaryl, and OR_8 wherein R_8 is C_{1-15} alkyl, C_{2-15} alkenyl, C_{2-15} alkynyl, C_{6-15} aryl, heteroaryl, or hydroxyl protecting group; and R_6 is hydrogen, C_{1-15} alkyl, C_{2-15} alkenyl, C_{2-15} alkynyl, C_{6-15} aryl, substituted C_{6-15} aryl, or heteroaryl; and

wherein substituted C_{6-15} aryl has the same meaning as in claim 1;

the contacting of said alcohol and oxazinone being carried out in the presence of a sufficient amount of an activating agent to cause the oxazinone to react with the alcohol to form a taxol derivative having a C-13 β-amido ester group which is suitable for use as an intermediate in the synthesis of taxol.

7. A process for the preparation of a taxol having the formula:



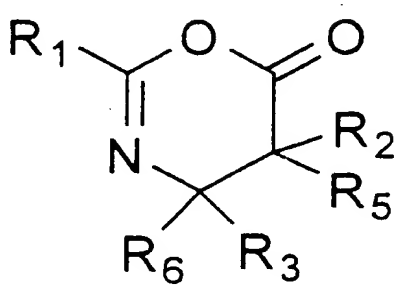
wherein

A and B are independently hydrogen or lower alkanoyloxy, alkenoyloxy, alkynoyloxy, or aryloyloxy or
A and B together form an oxo;
L and D are independently hydrogen or hydroxy or lower alkanoyloxy, alkenoyloxy, alkynoyloxy, or aryloyloxy;
E and F are independently hydrogen or lower alkanoyloxy, alkenoyloxy, alkynoyloxy, or aryloyloxy or;
E and F together form an oxo;
G is hydrogen or hydroxy or lower alkanoyloxy, alkenoyloxy, alkynoyloxy, or aryloyloxy or
G and M together form an oxo or methylene or
G and M together form an oxirane or
M and F together form an oxetane;
J is hydrogen, hydroxy, or lower alkanoyloxy, alkenoyloxy, alkynoyloxy, or aryloyloxy or
I is hydrogen, hydroxy, or lower alkanoyloxy, alkenoyloxy, alkynoyloxy, or aryloyloxy; or
I and J taken together form an oxo; and
K is hydrogen, hydroxy or lower alkoxy, alkanoyloxy, alkenoyloxy, alkynoyloxy, or aryloyloxy; and
P and Q are independently hydrogen or lower alkanoyloxy, alkenoyloxy, alkynoyloxy, or aryloyloxy or
P and Q together form an oxo; and
S and T are independently hydrogen or lower alkanoyloxy, alkenoyloxy, alkynoyloxy, or aryloyloxy or
S and T together form an oxo; and
U and V are independently hydrogen or lower alkyl, alkenyl, alkynyl, aryl, or substituted aryl; and
W is aryl, substituted aryl, lower alkyl, alkenyl, or alkynyl,

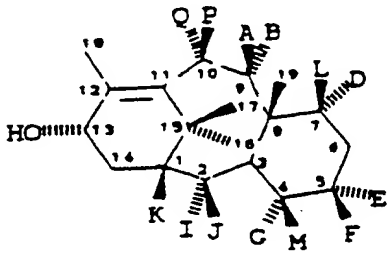
and wherein the alkyl groups contain 1 to 10 carbon atoms, the alkynyl groups contain 2 to 10 carbon atoms, the

alkynyl groups contain 2 to 10 carbon atoms, and the aryl groups contain 6 to 15 carbon atoms, comprising:

contacting an oxazinone of the formula:



wherein R_1 and R_3 are as defined in claim 1; and R_2, R_5 and R_6 are as defined in claim 6; with an alcohol of the formula:



wherein said A, B, D, E, F, G, I, J, K, L, M, P and Q are as defined above, the contacting of said oxazinone and said alcohol being carried out in the presence of a sufficient amount of an activating agent to cause the oxazinone to react with the alcohol to form a β-amido ester which is suitable for use as an intermediate in the synthesis of taxol, and converting said intermediate to taxol.

8. A process according to claim 6 or claim 7, wherein R_1 is C_{6-15} aryl, R_2 is OR_8 with R_8 being ethoxyethyl or 2,2,2-trichloroethoxymethyl, and R_3 is C_{6-15} aryl.

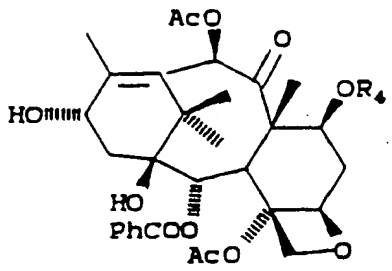
9. A process according to any one of claims 6 to 8, wherein R_1 and R_3 are phenyl, R_5 and R_6 are hydrogen, and R_2 is OR_8 with R_8 being a hydroxyl protecting group.

10. A process for the preparation of taxol which comprises contacting an alcohol having the taxane tetracyclic nucleus and a C-13 hydroxyl group with an oxazinone according to any one of claims 1 to 5,

the contacting of said alcohol and oxazinone being carried out in the presence of a sufficient amount of an activating agent to cause the oxazinone to react with the alcohol to form a β-amido ester which is suitable for use as an intermediate in the synthesis of taxol, and converting said intermediate to taxol.

11. A process according to any one of claims 6 to 10, wherein the hydroxyl protecting group is selected from acetals, ethers, esters, and carbonates.

12. A process according to any one of claims 6 to 11, wherein the alcohol has the formula:



wherein R_4 is a hydroxyl protecting group.

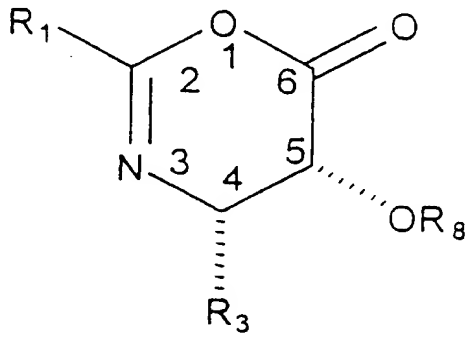
13. A process according to claim 12, wherein R_4 is selected from ethers, esters, carbonates and silyl groups.

14. A process according to any one of claims 6 to 13, wherein the activating agent is a tertiary amine.

15. A process according to claim 14, wherein the activating agent is triethyl amine, diisopropyl ethyl amine, pyridine, N-methyl imidazole, or 4-dimethylaminopyridine.

Patentansprüche

1. Oxazinon der Formel:



worin R_1 C_{6-15}-Aryl, substituiertes C_{6-15}-Aryl, Heteroaryl, C_{1-15}-Alkyl, C_{2-15}-Alkenyl, C_{2-15}-Alkinyl oder OR_7 ist, wobei R_7 C_{1-15}-Alkyl, C_{2-15}-Alkenyl, C_{2-15}-Alkinyl, C_{6-15}-Aryl oder Heteroaryl ist, R_8 Ethoxyethyl, 2,2,2-Trichlorethoxymethyl oder eine andere Hydroxyl-Schutzgruppe ist; und R3 Wasserstoff, C_{1-15}-Alkyl, C_{2-15}-Alkenyl C_{2-15}-Alkinyl, C_{6-15}-Aryl, substituiertes C_{6-15}-Aryl und Heteroaryl ist, wobei substituiertes C_{6-15}-Aryl ein C_{6-15}-Aryl bedeutet, das mit wenigstens einem Substituenten substituiert ist, der unter Alkanoxy, Hydroxy, Halogen, Alky, Aryl, Alkenyl, Acyl, Acyloxy, Nitro und Amido ausgewählt ist.

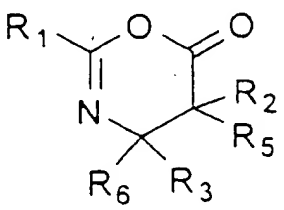
2. Oxazinon nach Anspruch 1, bei dem die Hydroxyl-Schutzgruppe aus der Gruppe ausgewählt ist, die aus Acetalen, Ethern, Estern und Carbonaten besteht.

3. Oxazinon nach Anspruch 1 oder Anspruch 2, bei dem R_1 Aryl ist, R_8 Ethoxyethyl oder 2,2,2-Trichlorethoxymethyl ist und R_3 C_{6-15}-Aryl ist.

4. Oxazinon nach einem der Ansprüche 1 bis 3, bei dem R_1 und R_3 Phenyl sind.

5. Die Enantiomeren und Diastereomeren eines Oxazinons nach einem der Ansprüche 1 bis 4.

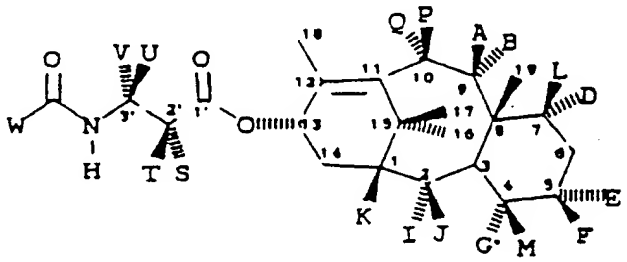
6. Verfahren zur Herstellung eines Taxol-Zwischenprodukts, bei dem man einen Alkohol mit dem tetrazyklischen Taxan-Kern und einer Hydroxylgruppe an C-13 mit einem Oxazinon der Formel:



in Berührung bringt, in der R_1 und R_3 wie in Anspruch 1 definiert sind; R_2 und R_5 unabhängig voneinander unter Wasserstoff, C_{1-15}-Alkyl, C_{2-15}-Alkenyl, C_{2-15}-Alkinyl, C_{6-15}-Aryl, substituiertem C_{6-15}-Aryl, Heteroaryl und OR_8 ausgewählt sind, wobei R_8 C_{1-15}-Akyl, C_{2-15}-Alkenyl, C_{2-15}-Alkinyl, C_{6-15}-Aryl, Heteroaryl oder eine Hydroxyl-Schutzgruppe ist, und R_6 Wasserstoff, C_{1-15}-Alkyl, C_{2-15}-Alkenyl, C_{2-15}-Alkinyl, C_{6-15}-Aryl, substituiertes C_{6-15}-Aryl oder Heteroaryl bedeutet und wobei substituiertes C_{6-15}-Aryl die gleiche Bedeutung wie in Anspruch 1 hat,

wobei die Berührung des Alkohols mit dem Oxazinon in Gegenwart einer genügenden Menge eines Aktivierungsmittels durchgeführt wird, um die Umsetzung des Oxazinons mit dem Alkohol unter Bildung eines Taxol-Derivates mit einer β-Amidoester-Gruppe an C-13 zu veranlassen, das als Zwischenprodukt bei der Taxolsynthese geeignet ist.

7. Verfahren zur Herstellung eines Taxols mit der Formel:



worin

A und B unabhängig voneinander Wasserstoff oder niederes Alkanoyloxid, Alkenoyloxid, Alkinoyloxid oder Aryloyloxid sind oder

A und B zusammen Oxo bilden;

L und D unabhängig voneinander Wasserstoff oder Hydroxy oder niederes Alkanoyloxy, Alkenoyloxy, Alkinoyloxy oder Aryloyloxy sind;

E und F unabhängig voneinander Wasserstoff oder niederes Alkanoyloxy, Alkenoyloxy, Alkinyloxy oder Aryloyloxy sind oder

E und F zusammen Oxo bilden;

G Wasserstoff oder Hydroxy oder niederes Alkanoyloxy, Alkenoyloxy, Alkinoyloxy oder Aryloyloxy ist oder

G und M zusammen Oxo oder Methylen bilden oder

G und M zusammen ein Oxiran bilden oder

M und F zusammen ein Oxetan bilden;

J Wasserstoff, Hydroxy oder niederes Alkanoyloxy, Alkenoyloxy, Alkinoyloxy oder Aryloyloxy ist oder

I Wasserstoff, Hydroxy oder niederes Alkanoyloxy, Alkenoyloxy, Alkinoyloxy oder Aryloyloxy ist; oder

I und J zusammen Oxo bilden; und

K Wasserstoff, Hydroxy oder niederes Alkoxy, Alkanoyloxy, Alkenoxloxy, Alkinoyloxy oder Aryloyloxy ist; und

P und Q unabhängig voneinander Wasserstoff oder niederes Alkanoyloxy, Alkenoyloxy, Alkinoyloxy oder Aryloyloxy sind oder

P und Q zusammen Oxo bilden; und

S und T unabhängig voneinander Wasserstoff oder niederes Alkanoyloxy, Alkenoyloxy, Alkinoyloxy oder Ary-

loyloxy sind oder

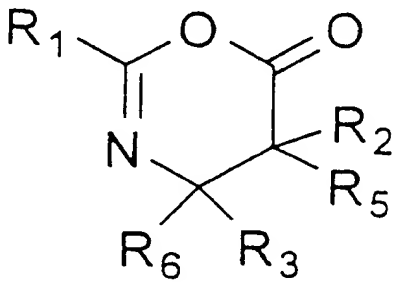
S und T, zusammen Oxo bilden; und

U und V unabhängig voneinander Wasserstoff oder niederes Alkyl, Alkenyl, Alkinyl, Aryl oder substituiertes Aryl sind; und

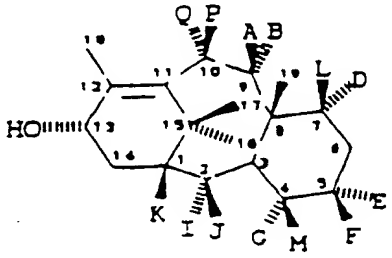
W Aryl, substituiertes Aryl, niederes Alkyl, Alkenyl oder Alkinyl ist,

und worin die Alkylgruppen 1 bis 10 Kohlenstoffatome, die Alkenyl-Gruppen 2 bis 10 Kohlenstoffatome, die Alkinyl-Gruppen 2 bis 10 Kohlenstoffatome und die Aryl-Gruppen 6 bis 15 Kohlenstoffatome enthalten,

bei dem man ein Oxazinon der Formel:



worin R_1 und R_3 wie in Anspruch 1 definiert sind und R_2, R_3 und R_6 wie in Anspruch 6 definiert sind, mit einem Alkohol der Formel:



in Kontakt bringt, worin A, B, D, E, F, G, I, J, K, L, M, P und Q die oben definierte Bedeutung haben, wobei die Berührung des Oxazinons mit dem Alkohol in Gegenwart einer ausreichenden Menge eines Aktivierungsmittels folgt, um die Umsetzung des Oxazinons mit dem Alkohol unter Bildung eines β-Amidoesters zu veranlassen, der sich zur Verwendung als Zwischenprodukt in der Taxol-Synthese eignet, und das genannte Zwischenprodukt zu Taxol umsetzt.

8. Verfahren nach Anspruch 6 oder Anspruch 7, bei dem R_1 C_{6-15}-Aryl ist, R_2 die Bedeutung von OR_8 hat, wobei R_8 Ethoxyethyl oder 2,2,2-Trichlorethoxymethyl ist, und R_3 die Bedeutung von C_{6-15}-Aryl hat.

9. Verfahren nach einem der Ansprüche 6 bis 8, bei dem R_1 und R_3 Phenyl sind, R_5 und R_6 Wasserstoff sind und R_2 die Bedeutung von OR_8 hat, wobei R_8 eine Hydroxyl-Schutzgruppe ist.

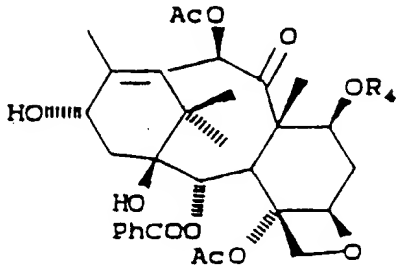
10. Verfahren zur Herstellung von Taxol, bei dem man einen Alkohol mit dem tetrazyklischen Taxan-Kern und einer Hydroxylgruppe an C-13 mit einem Oxazinon nach einem der Ansprüche 1 bis 5 in Kontakt bringt,

wobei die Kontaktierung des genannten Alkohols und Oxazinons in Gegenwart einer ausreichenden Menge eines Aktivierungsmittels erfolgt, um die Umsetzung des Oxazinons mit dem Alkohol unter Bildung eines β-Amidoesters zu veranlassen, der zur Verwendung als Zwischenprodukt bei der Taxol-Synthese geeignet ist,

und das genannte Zwischenprodukt zu Taxol umsetzt.

11. Verfahren nach einem der Ansprüche 6 bis 10, bei dem man die Hydroxyl-Schutzgruppe unter Acetalen, Ethern, Estern und Carbonaten auswählt.

12. Verfahren nach einem der Ansprüche 6 bis 11, bei dem der Alkohol die Formel:



hat, worin R_4 eine Hydroxyl-Schutzgruppe ist.

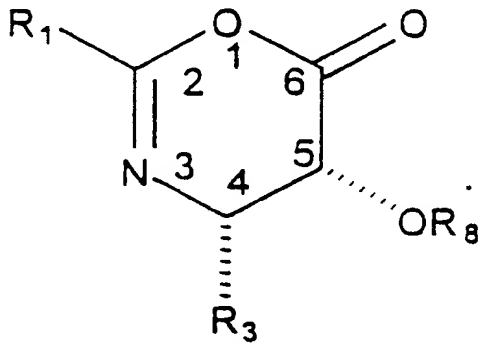
13. Verfahren nach Anspruch 12, bei dem R_4 unter Ethern, Estern, Carbonaten und Silylgruppen ausgewählt ist.

14. Verfahren nach einem der Ansprüche 6 bis 13, bei dem das Aktivierungsmittel ein tertiäres Amin ist.

15. Verfahren nach Anspruch 14, bei dem das Aktivierungsmittel Triethylamin, Diisopropylethylamin, Pyridin, N-Methylimidazol oder 4-Dimethylaminopyridin ist.

Revendications

1. Oxazinone de formule :



dans laquelle R_1 est un groupe aryle en C_{6-15}, un groupe aryle substitué en C_{6-15}, un groupe hétéroaryle, un groupe alkyle en C_{1-15}, un groupe alcényle en C_{2-15}, un groupe alcynyle en C_{2-15} ou OR_7, dans lequel R_7 est un groupe alkyle en C_{1-15}, un groupe alcényle en C_{2-15}, un groupe alcynyle en C_{2-15}, un groupe aryle en C_{6-15} ou un groupe hétéroaryle; R_8 est un groupe éthoxyéthyle, 2,2,2-trichloroéthoxyméthyle ou une autre groupe protégeant la fonction hydroxy; et R_3 est un atome d'hydrogène, un groupe alkyle en C_{1-15}, un groupe alcényle en C_{2-15}, un groupe alcynyle en C_{2-15}, un groupe aryle en C_{6-15}, un groupe aryle substitué en C_{6-15} ou un groupe hétéroaryle; où un groupe aryle substitué en C_{6-15} signifie un groupe aryle en C_{6-15} substitué par au moins un substituant choisi parmi les groupes alcanoxy, hydroxy, atome d'halogène, groupes alkyle, aryle, alcényle, acyle, acyloxy, nitro et amido.

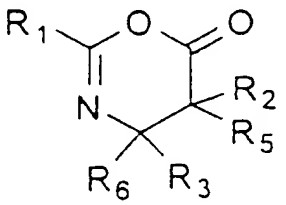
2. Oxazinone suivant la revendication 1, dans laquelle le groupe protégeant la fonction hydroxy est choisi dans le groupe consistant en acétals, éthers, esters et carbonates.

3. Oxazinone suivant les revendications 1 ou 2, dans laquelle R_1 est un groupe aryle, R_8 est un groupe éthoxyéthyle ou 2,2,2-trichloroéthoxyméthyle et R_3 est un groupe aryle en C_{6-15}.

4. Oxazinone suivant les revendications 1 à 3, dans laquelle R_1 et R_3 sont un groupe phényle.

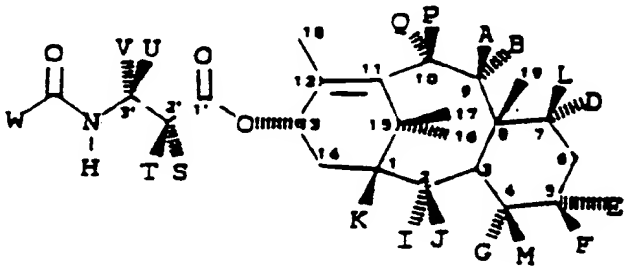
5. Enantiomères et diastéréoisomères d'une oxazinone suivant les revendications 1 à 4.

6. Procédé pour la préparation d'un intermédiaire de taxol comprenant la mise en contact d'un alcool ayant le noyau tétracyclique du taxane et un groupe hydroxy en C13 avec une oxazinone ayant la formule :



dans laquelle R_1 et R_3 sont tels que définis dans la revendication 1; R_2 et R_5 sont indépendamment choisis parmi un atome d'hydrogène, un groupe alkyle en C_{1-15}, un groupe alcényle en C_{2-15}, un groupe alcynyle en C_{2-15}, un groupe aryle en C_{6-15}, un groupe aryle substitué en C_{6-15}, ùn groupe hétéroaryle et OR_8, dans lequel R_8 est un groupe alkyle en C_{1-15}, un groupe alcényle en C_{2-15}, un groupe alcynyle en C_{2-15}, un groupe aryle en C_{6-15}, un groupe hétéroaryle ou un groupe protégeant la fonction hydroxy; et R_6 est un atome d'hydrogène, un groupe alkyle en C_{1-15}, un groupe alcényle en C_{2-15}, un groupe alcynyle en C_{2-15}, un groupe aryle en C_{6-15}, un groupe aryle substitué en C_{6-15} ou un groupe hétéroaryle; et où un groupe aryle substitué en C_{6-15} est tel que défini dans la revendication 1; la mise en contact de cet alcool et de cette oxazinone étant conduite en présence d'une quantité suffisante d'un agent d'activation pour provoquer la réaction de l'oxazinone avec l'alcool afin de former un dérivé du taxol ayant un groupe β-amido ester en C13 qui est utilisable comme intermédiaire dans la synthèse de taxol.

7. Procédé pour la préparation d'un taxol ayant la formule :

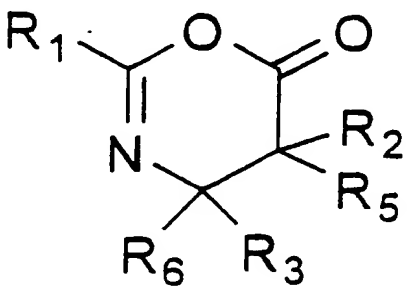


dans laquelle :

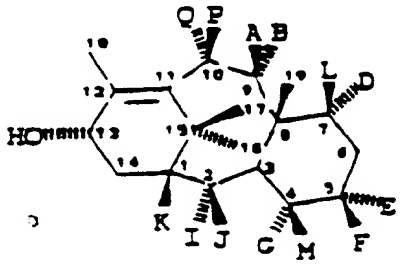
A et B	sont indépendamment un atome d'hydrogène ou un groupe alcanoyloxy, alcénoyloxy, alcynoyloxy inférieur ou un groupe aryloyloxy, ou
A et B	forment ensemble un groupe oxo;
L et D	sont indépendamment un atome d'hydrogène ou un groupe hydroxy ou un groupe alcanoyloxy, alcénoyloxy, alcynoyloxy inférieur ou un groupe aryloyloxy,
E et F	sont indépendamment un atome d'hydrogène ou un groupe alcanoyloxy, alcénoyloxy, alcynoyloxy inférieur ou un groupe aryloyloxy, ou
E et F	forment ensemble un groupe oxo;
G	est un atome d'hydrogène ou un groupe hydroxy ou un groupe alcanoyloxy, alcénoyloxy, alcynoyloxy inférieur ou un groupe aryloyloxy, ou
G et M	forment ensemble un groupe oxo ou méthylène, ou
G et M	forment ensemble un groupe oxirane, ou
M et F	forment ensemble un groupe oxétane;
J	est un atome d'hydrogène ou un groupe hydroxy, ou un groupe alcanoyloxy, alcénoyloxy, alcynoyloxy inférieur ou un groupe aryloyloxy, ou
I	est un atome d'hydrogène ou un groupe hydroxy ou un groupe alcanoyloxy, alcénoyloxy, alcynoyloxy inférieur ou un groupe aryloyloxy, ou

I et J	forment ensemble un groupe oxo; et
K	est un atome d'hydrogène ou un groupe hydroxy ou un groupe alcanoyloxy, alcénoyloxy, alcynoyloxy inférieur ou un groupe aryloyloxy; et
P et Q	sont indépendamment un atome d'hydrogène ou un groupe alcanoyloxy, alcénoyloxy, alcynoyloxy inférieur ou un groupe aryloyloxy, ou
P et Q	forment ensemble un groupe oxo; et
S et T	sont indépendamment un atome d'hydrogène ou un groupe alcanoyloxy, alcénoyloxy, alcynoyloxy inférieur ou un groupe aryloyloxy, ou
S et T	forment ensemble un groupe oxo; et
U et V	sont indépendamment un atome d'hydrogène ou un groupe alkyle, alcényle, alcynyle inférieur, aryle ou aryle substitué; et
W	est un groupe aryle, aryle substitué, alkyle, alcényle ou alcynyle inférieur,

et dans laquelle les groupes alkyles contiennent 1 à 10 atomes de carbone, les groupes alcényles contiennent 2 à 10 atomes de carbone, les groupes alcynyles contiennent 2 à 10 atomes de carbone et les groupes aryles contiennent 6 à 15 atomes de carbone, comprenant
la mise en contact d'une oxazinone de formule :



dans laquelle R_1 et R_3 sont tels que définis dans la revendication 1; R_2, R_5 et R_6 sont tels que définis dans la revendication 6;
avec un alcool de formule :



dans laquelle ces A, B, D, E, F, G, I, J, K, L, M; P et Q sont tels que définis plus haut, la mise en contact de cette oxazinone et de cet alcool étant conduite en présence d'une quantité suffisante d'un agent d'activaton pour provoquer la réaction de l'oxazinone avec l'alcool afin de former un β-amido ester qui est utilisable comme intermédiaire dans la synthèse d'un taxol, et la conversion de cet intermédiaire en taxol.

8. Procédé suivant les revendications 6 ou 7, dans lequel R_1 est un groupe aryle en C_{6-15}, R_2 est OR_8 dans lequel R_8 est un groupe éthoxyéthyle ou 2,2,2-trichloroéthoxyméthyle, et R_3 est un groupe aryle en C_{6-15}.

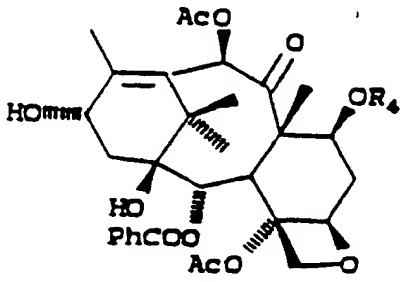
9. Procédé suivant l'un quelconque des revendications 6 à 8, dans lequel R_1 et R_3 sont un groupe phényle, R_5 et R_6 sont un atome d'hydrogène, et R_2 est OR_8 dans lequel R_8 est un groupe protégeant la fonction hydroxy.

10. Procédé pour la préparation de taxol, qui comprend la mise en contact d'un alcool ayant le noyau tétracyclique du taxane et un groupe hydroxy en C13 avec une oxazinone suivant l'une quelconque des revendications 1 à 5, la mise

en contact de cette oxazinone et de cet alcool étant conduite en présence d'une quantité suffisante d'un agent d'activation pour provoquer la réaction de l'oxazinone avec l'alcool afin de former un β-amido ester qui est utilisable comme intermédiaire dans la synthèse d'un taxol, et la conversion de cet intermédiaire en taxol.

11. Procédé suivant l'une quelconque des revendications 6 à 10, dans lequel le groupe protégeant la fonction hydroxy est choisi parmi des acétals, des éthers, des esters et des carbonates.

12. Procédé suivant l'une quelconque des revendications 6 à 11, dans lequel l'alcool a la formule :



dans laquelle R_4 est un groupe protégeant la fonction hydroxy.

13. Procédé suivant la revendication 12, dans lequel R_4 est choisi parmi des éthers, des esters, des carbonates et des groupes silyles.

14. Procédé suivant l'une quelconque des revendications 6 à 13, dans lequel l'agent d'activation est une amine tertiaire.

15. Procédé suivant la revendication 14, dans lequel l'agent d'activation est la triéthylamine, la diisopropyléthyl amine, la pyridine, le N-méthyl imidazole ou la 4-diméthylaminopyridine.